Hemodynamic latency is associated with reduced intelligence: an fMRI DCM study of aging, cerebrovascular integrity, and cognitive ability

Running Title: Hemodynamic latency is associated with reduced intelligence

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Abstract:

Changes in neurovascular coupling are associated with both Alzheimer's disease and vascular dementia in later life, but this may be confounded by cerebrovascular risk. We hypothesized that hemodynamic latency would be associated with reduced cognitive functioning across the lifespan, holding constant demographic and cerebrovascular risk.

In 387 adults aged 18-85 (mean = 48.82), dynamic causal modeling was used to estimate the hemodynamic response function in the left and right V1 and V3 regions of the visual cortex in response to a simple checkerboard stimulus with minimal cognitive demands. The hemodynamic latency (transit time) in the visual cortex was used to predict general cognitive ability (Full-Scale IQ), controlling for demographic variables (age, race, education, socioeconomic status) and cerebrovascular risk factors (hypertension, alcohol use, smoking, high cholesterol, BMI, type 2 diabetes, cardiac disorders).

Increased hemodynamic latency in the visual cortex predicted impaired cognitive function ($p<0.05$), holding constant demographic and cerebrovascular risk. Increased alcohol use was associated with reduced overall cognitive function (Full Scale IQ 2.8 pts, $p<0.05$), while cardiac disorders (Full Scale IQ 3.3 IQ pts; $p<0.05$), high cholesterol (Full Scale IQ 3.9 pts; $p<0.05$), and years of education (2 IQ pts/year; $p<0.001$) were associated with higher general cognitive ability. Increased hemodynamic latency was associated with reduced executive functioning ($p<0.05$) as well as deficits in verbal concept formation ($p<0.05$) and the ability to synthesize and analyze abstract visual information ($p<0.01$).

Hemodynamic latency is associated with reduced cognitive ability across the lifespan, independently of other demographic and cerebrovascular risk factors.

Introduction

The relationship between cerebral blood flow (CBF) and local neural activity, known as neurovascular coupling (NVC), is altered in neurocognitive disorders such as Alzheimer's disease and other dementias (Østergaard et al., 2013; Wierenga et al., 2012; Wierenga, Hays, & Zlatar, 2014). However, this relationship may be mediated by cerebrovascular risk factors such as hypertension (Nobili et al., 1993), cholesterol (Notkola et al., 1998), alcohol abuse (Anttila et al., 2004) and smoking (Chang, Zhao, Lee, & Ganguli, 2012), which are also associated with cognitive ability. Moreover, mortality increases with cerebrovascular risk, so studies in elderly populations – assessing the relationship between cerebrovascular risk and cognitive ability – may be subject to survival bias (Johnston & Hauser, 2010); the "unhealthy" high-risk population is deceased prior to the onset of dementia, leaving only "healthy" high-risk individuals for comparison with all low-risk individuals (Chang et al., 2012). Cross-lifespan studies may better assess whether cerebrovascular risk is associated with cognitive decline by including younger populations. We hypothesized that the latency of the hemodynamic response function would be associated with reduced cognitive functioning, above and beyond all other demographic and cerebrovascular risk factors.

Cerebral blood flow differences are observed with impaired cognitive functioning (Buckner, Snyder, Sanders, Raichle, & Morris, 2000) and increased age (Ances et al., 2009; Buckner et al., 2000; Gröschel et al., 2007; Riecker et al., 2003), with hemodynamic changes preceding cognitive decline (Østergaard et al., 2013; Wierenga et al., 2012; Wierenga et al., 2014). NVC may be altered in hypertension, ischemic stroke, and Alzheimer's disease, as discussed in Girouard et al. (Girouard & Iadecola, 2006). Disruption in NVC has been found throughout the brain following lacunar stroke (Pineiro, Pendlebury, Johansen-Berg, & Matthews, 2002) and in patients with disrupted cerebrovascular reserve capacity due to intra/extracranial stenosis (Hamzei, Knab, Weiller, & Röther, 2003). Stroke is a risk factor for both Alzheimer's disease (Zhou et al., 2015) and other dementias (Kuźma et al., 2018). Subjects with Mild Cognitive Impairment – who also had CBF deficits – converted more rapidly to Alzheimer's disease (Hirao et al., 2005), while other work suggests APOE-4 genotype and vascular health may be interacting risk factors for cognitive decline (Anstey, Lipnicki, & Low, 2008; Breteler, 2000; Evans et al., 2000; Evans et al., 2004; Jarvik et al., 1995; Notkola et al., 1998; Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009).

The association between NVC and cognitive ability may be mediated by cerebrovascular risk, since cerebrovascular risk factors alter cerebral blood flow. CBF is reduced in patients with untreated hypertension compared to those with treated hypertension (Nobili et al., 1993). Hypertension is associated with reduced cognitive performance (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Robbins, Elias, Elias, & Budge, 2005), and mid-life hypertension increases the risk of cognitive impairment in older age (Birkenhäger, Forette, Seux, Wang, & Staessen, 2001; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). However, hypertension treatment alone does not decrease the risk of dementia in older adults (McGuinness, Todd, Passmore, & Bullock, 2009; Novak & Hajjar, 2010). Other clinical measures also support the association between vascular health and cognitive ability. High cholesterol affects cognitive domains differently, with increases seen in Block Design, but decreases in crystallized intelligence using the Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Muldoon, Ryan, Matthews, & Manuck, 1997). High cholesterol increases the risk for atherosclerosis (de la Torre, 2012), which is also a risk factor for dementia (Dolan et al., 2010). High midlife total serum cholesterol is associated with an increased risk of AD and any

dementia, but not vascular dementia (Anstey et al., 2008; Solomon et al., 2009). Total serum cholesterol decreased in those who subsequently developed AD (Notkola et al., 1998), with potential decreases in blood pressure also preceding disease onset (Breteler, 2000).

Arterial Spin Labeling is commonly used to measure cerebral perfusion, yet has poor temporal resolution making it suboptimal for evaluating NVC. Estimates of NVC are also obtainable through fMRI using Bayesian approaches such as Dynamic Causal Modeling (DCM) (Friston, Harrison, & Penny, 2003). DCM is a spatiotemporal, generative network model that estimates coupling within and among regions of interest in the brain, and how regions respond to stimuli. Because DCM uses a generative (i.e., forward) model, it also provides posterior estimates of the parameters governing the regional hemodynamic response function (HRF). The HRF is the regional Blood Oxygenation Level Dependent (BOLD) response generated from a brief peripheral stimulus, created through a sequence of vascular and metabolic dynamics (Buxton, Uludağ, Dubowitz, & Liu, 2004; Friston, Mechelli, Turner, & Price, 2000; Wan et al., 2006). The model of the BOLD signal – implemented in DCM – includes several parameters that shape the haemodynamic response. The latency parameter of the HRF, τ has the effect illustrated in Figure 1, of both changing the overall speed of the response and affecting the relative magnitudes of the initial positive BOLD signal change and the negative response, following the end of the stimulus (post-stimulus undershoot). In DCM's haemodynamic model, τ is the mean transit time of blood; i.e., the average time blood takes to traverse the venous compartment. The transit time corresponds to the ratio of resting blood volume V_0 to resting blood flow F_0: $\tau = V_0/F_0$. This is the model parameter most closely tied to the concept of the speed of the response and the time to reach the response peak.

NVC is altered in the visual cortex in Alzheimer's disease (Mentis et al., 1996).   The visual cortex, perfused by the posterior cerebral artery, contains the highest density of neurons in the cortex (Leuba & Kraftsik, 1994). Changes in posterior cerebral blood flow were previously mapped to aging, and were associated with fibrinogen and indicators of carotid atherosclerosis (Claus et al., 1998). Previously, effective connectivity changes in the visual cortex were identified using DCM in early Alzheimer's disease (Rytsar, Fornari, Frackowiak, Ghika, & Knyazeva, 2011) using a blocked checkerboard stimulus. Changes in the hemodynamic response function's amplitude were also seen between older and younger subjects with a flickering checkerboard task, suggesting this stimulus is sensitive to age-related BOLD changes (Ances et al., 2009; Buckner et al., 2000). Age-related HRF changes outside the visual cortex in the motor and auditory cortices suggest that, similar to CBF, the HRF evolves across the lifespan (West et al., 2019).

Analyses of cerebrovascular risk and cognitive ability in elderly cohorts may be confounded by competing risk and survival bias (Chang et al., 2012), where subjects with higher cerebrovascular risk are likely to die earlier before dementia onset. Given the changes in NVC and CBF associated with neurocognitive disorders in older adults, we hypothesized that age-abnormal NVC may predict reduced cognition across the lifespan and that these changes would be unique to other cerebrovascular risk factors. Because multiple areas of the brain are essential for the functional integration that underwrites higher cognitive function, this hypothesis was tested using a passive visual stimulus (flickering checkerboard), which requires minimal cognitive effort and has no known relation to cognitive performance. The occipital lobe, activated by visual stimuli, is one of

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the first areas of the brain to myelinate – and one of the final areas to degenerate in Alzheimer's disease – which helps to decouple the impact of neurodegeneration and cerebral hemodynamics in aging populations (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006). In 387 adults aged 18-85, we used DCM to estimate the HRF in the visual cortex in response to a flickering checkerboard stimulus; similar to the approach of Rytsar et al. (Rytsar et al., 2011). Ances et al. previously found that the duration of the HRF undershoot was increased in elderly populations – but not the magnitude of this undershoot (Ances et al., 2009), suggesting that hemodynamic latency may change with age. Collectively, we asked whether hemodynamic latency predicts global and specific cognitive abilities, independent of all other demographic and cerebrovascular risk factors, across the lifespan.

Methods:

Subjects: The Nathan Kline Institute, Rockland Sample (NKI-RS) sample is an ongoing initiative aimed at creating a large-scale (N>1000) community sample across the lifespan, taken from subjects residing in Rockland County, NY (Nooner et al., 2012). All subjects provided written informed consent after receiving a complete description of the study; this study was approved by the Institutional Review Board and adheres to US Federal Policy for the Protection of Human Subjects. Subjects in NKI were excluded for any of the following criteria: history of stroke, insufficient fMRI visual cortex activation, excessive measured fMRI motion > 3 mm, missing clinical or medical history data, and insufficient scan coverage. After exclusion, there remained 387 subjects who had both full clinical information and suitable fMRI and MRI scans for subsequent neurocognitive analyses, described in more detail in the Supplementary Table 1 in the Appendix.

Subjects completed a medical history exam and a series of functional and structural MRI scans, described further in (Nooner et al., 2012). Participants were assessed for alcohol and tobacco use with the NIDA quick screen (Wu et al., 2016). Additionally, neuropsychological batteries were administered including the Wechsler Abbreviated Scale of Intelligence (WASI-II; (Stano, 2004)), the Delis-Kaplan executive function system (DKEFS) (Sue Baron, 2004), and the Rey auditory verbal learning test (RAVLT; (Schmidt, 1996)). These three protocols were chosen for their sensitivity to measures cognitive abilities typically affected by vascular health, and are described further in the Appendix. Full demographic and clinical assessment summaries are provided in the Appendix: Table 1.

Subjects were scanned using fMRI in a blocked design using a checkerboard stimulus consisting of three repetitions of a 20s fixation block and a 20s flickering checkerboard block. Scans were repeated using two different TRs: 1400 ms. The following parameters were used: TR = 1400 ms; TE = 30 ms; flip angle = 65 deg; voxel size = 2 x 2 x 2 mm isotropic; number of slices = 64. TR = 645 ms; TE = 30 ms; flip angle = 60 deg; voxel size = 3 x 3 x 3 mm. isotropic; number of slices = 40. Anatomical T1 images were scanned using MPRAGE (magnetization-prepared rapid acquisition with gradient echo) sequence with the following parameters: TR = 1900 ms; TE = 2.52 ms; flip angle = 90 degrees; voxel size = 1 x 1 x 1 mm (isotropic).

fMRI pre-processing was performed with SPM12 (Wellcome Centre for Human Neuroimaging,

London, UK) using standard SPM procedures (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011): realignment to correct for head movement, normalization to MNI space and convolution with an isotropic Gaussian kernel (FWHM=9 mm) to increase the signal to noise ratio. Single subject analyses were performed using the General Linear Model, removing signal drift with a high-pass filter. Statistical parametric maps for the checkerboard contrast (i.e., responses to visual stimulation) were obtained using the appropriate contrast under a general (convolution) linear model. Inferences about Group responses were adjusted from comparisons using Random Field Theory. Visually responsive regions were identified using clusters with a height threshold of p<0.005 (t-test) and extent threshold k>30 contiguous voxels.

Dynamic Causal Modeling:
Four regions of interest were selected for further analyses based on the SPM analyses identifying responses to checkerboard stimulus: V1 Left, V1 Right, V3 Left, and V3 Right. These regions also have established roles in processing basic visual stimuli (Dumoulin & Wandell, 2008; Lang et al., 1998; Rytsar et al., 2011; Smith, Greenlee, Singh, Kraemer, & Hennig, 1998) with V3 regions providing higher-order processing than the primitive V1 region. Using the Wang visual cortex atlas (Wang, Mruczek, Arcaro, & Kastner, 2014), non-overlapping masks of these four regions were created and then applied to each subject's SPM. Regional responses were summarized – for subsequent DCM analysis – with the first principal component of all voxel time series within a sphere of 4 mm radius, centered on the individual local SPM maxima within each atlas mask.

Following (Rytsar et al., 2011), which used a simple flickering visual stimulus, sixteen competing models for effective (between region) connectivity were compared to ensure the optimal balance between model complexity and accuracy, as shown in Figure 2. Driving or visual inputs were restricted to the early visual regions. For completeness, Bayesian model selection (BMS) was performed using two approaches: (i) fixed effects BMS; namely, pulling the log-model evidence (i.e., the negative free energy) over subjects for each model (Friston et al., 2003) and (ii) random effects BMS (Rigoux, Stephan, Friston, & Daunizeau, 2014; Stephan, Penny, Daunizeau, Moran, & Friston, 2009). After selecting the optimal connectivity model, five candidate models for additional modulatory effects were considered; where modulatory effects represent the interaction between the effective connectivity and the driving inputs. These modulatory effects model the effects of driving inputs (i.e. visual stimulation) on connectivity among regions – in addition to direct effects on regional activity. Bayesian model selection of the best modulatory model used the same approach above.

We tested our hypotheses by using subject-specific estimates of haemodynamic parameters from the DCM as independent variables to predict cognition (dependent variable), while controlling for both demographic and cerebrovascular risk factors. Our primary hypothesis was that longer hemodynamic latency (transit time) in visual regions would be associated with lower cognitive ability, after adjusting for all other demographic and cerebrovascular risk factors. Because of the sampling resolution, other hemodynamic-specific DCM methods were not feasible (Heinzle, Koopmans, den Ouden, Raman, & Stephan, 2016).

This hypothesis was tested using a general linear model (in R). The WASI full-scale IQ composite score was used as the primary outcome measure of global cognitive ability, because it provides a

comprehensive average over several cognitive domains. Demographic covariates – used to explain global cognitive ability – included age, gender, race, socioeconomic status, years of education, and an interaction effect between race and socioeconomic status. Cerebrovascular risk factors included hypertension, BMI, smoking status, heavy alcohol use, high cholesterol, Type 2 Diabetes, and an indicator variable for "cardiac disorders", including history of any of the following conditions: history of heart attack, coronary artery disease, heart valve disease, and arrhythmia. Subjects with a history of stroke were excluded from the analysis. Heavy alcohol use was defined as having *any* positive number of heavy drinking days according to the NIDA- Quick screen question: "In the past year, how often have you used alcohol? For men, 5 or more drinks a day. For women, 4 or more drinks a day."

Posthoc analyses assessed which specific cognitive domains are most associated with hemodynamic latency, since the WASI captures multiple domains of intelligence. The demographic, cerebrovascular, and regional hemodynamic parameters were used to predict domain measures of executive functioning, verbal fluency, and matrix reasoning, among others described in Appendix Table 2. When available, both raw and scaled scores were tested to assess the consistency of our findings.

Additionally, we assessed whether the hemodynamic latency changed with age, following the findings of (West et al., 2019). Bayesian Parameter Averaging (BPA) was used to compute the transit time for each region of interest in young and old subjects. BPA provides posterior estimates of group means and variances for transit and decay parameters, for each region, weighted by the precision of subject specific estimates. Subjects with suitable fMRI scans and age information (n=599) from the larger sample were split into those with age greater or equal to (n=168) and less (n=431) than 60 to evaluate BPA of hemodynamic latency. This sample includes those subjects previously omitted for incomplete neurocognitive assessments. The BPA posterior over group means provides a direct Bayesian characterization of group effects, in terms of Bayesian credible intervals.

Finally, we replicated the earlier findings of (Rytsar et al., 2011), which identified weakened effective connectivity (and its modulation) in early Alzheimer's disease. Within later middle-aged adults aged 50-65 who did not have any clinical diagnoses of AD, we assessed whether effective connectivity differed between high cognitive performers and low cognitive performers. The SRS was selected as the measure of cognitive performance, since it was the domain of the WASI best predicted by the hemodynamic latency in the entire population. Within the 50-65 age range, subjects were partitioned into two groups according to whether they were in the bottom or top twentieth percentile for Similarities Raw Score (SRS) within the sample for subjects of that age. The resulting sample sizes were n=20 for small SRS values (5 male, 15 female) and n=21 for high SRS values (5 male, 16 female). Group effects were tested using a three-way mixed effects ANOVA model for both the effective connections and modulatory effects, within the model selected by BMS. This approach is similar to the Parametric Empirical Bayes Approach by permitting to characterize inter-subject variability in neural circuitry(Zeidman et al., 2019). Factors included in this model included group (high and low SRS values), hemisphere of the connection (L/R), whether or not the connection crossed a hemisphere (Y/N), and the regional topography of the connection (V1 ↔ V3, V1 ↔ V1, V3 ↔ V3 for intrinsic connections; V1 ↔ V3, V3 ↔ V3 for

modulatory effects). The mixed-effects ANOVA model corrects for multiple comparisons by treating the subject as a random effect, with other covariates modeled as fixed effects.

Results

Fixed and random effects Bayesian model selection yielded consistent results: for both of these approaches, Model C1 was optimal. After selection of the optimal effective connectivity model, modulatory models were also compared. Both fixed and random effects BMS yielded M5 as best and M4 as second best. Thus, the combined model of C1-M5 was selected to provide estimates the of hemodynamic parameters.

The analysis of between subject effects using a general linear model found that hemodynamic latency in the V3 Left and V3 Right regions were associated with reduced cognitive ability (full-scale IQ composite score, $p<0.05$). Posthoc analyses showed that alcohol use was also associated with reduced IQ (2.8 pts, $p<0.05$) while cardiac disorders (3.3 IQ pts; $p<0.05$), high cholesterol (3.9 pts; $p<0.05$), and years of education (2 IQ pts/year; $p<0.001$) were associated with higher general cognitive ability as shown in Table 1. For the V3 region, specific domain changes were found within WASI-II Similarities Raw Score ($p<0.001$), D-KEFS Category Fluency, Tower (Total Achievement Score), Trails Test (Motor Speed, Letter Sequencing) and Word Context, and RAVLT (Delay Recall- total correct), as shown in the Appendix.

Bayesian Parameter Averaging (BPA) was used to characterize age-related differences in transit and decay parameters for each region of interest. Subjects with suitable fMRI and age data (n=599) from the larger sample were partitioned into those with age >= 60 (n=168) and age <60 (n=431). This sample is larger than the primary analyses because it includes subjects who may have had incomplete neuropsychological assessments. The BPA estimates group means (and variances) for transit and decay parameters for each region. As shown in Figure 3, age-related differences were most marked for the transit and decay parameters in both left and right V1, with adults above the age of 60 exhibiting larger transit and decay values than younger subjects. It can be clearly seen that the older subjects have a group mean that is outside the 95 % credible interval for the younger subjects (and *vice versa*).

To replicate the earlier findings of (Rytsar et al., 2011), we additionally assessed whether effective connectivity (and its modulation) differed between high and low cognitive performers using a mixed-effects ANOVA in late-middle-aged adults (50-65-year-olds). Effective connectivity involving V3 showed a significant effect of group (estimated effect -0.142, $p < 0.005$), and the cross hemisphere connectivity showed a significant interaction with group (estimated effect -0.123, $p < 0.05$). A chi-squared test was performed to confirm that the addition of interaction effects was significant ($p < 0.03$). For modulatory effects, the V3 connections showed a significant effect of group (estimated effect -0.122, $p < 0.02$). Full model parameters are provided in Figure 4.

Discussion:

Altered neurovascular coupling (NVC) is one of several possible pathways connecting cardiovascular risk factors to cognitive decline later in life (reviewed by (Novak, 2012)) Our study found that increased hemodynamic latency – as measured in the visual cortex – may be associated with reduced cognition in a healthy sample across the lifespan. Specifically, using hemodynamic parameters from V1 and V3 regions that best explain the response to a flickering checkboard, we confirmed that changes in hemodynamic latency predicted cognitive ability, above and beyond all other demographics and cerebrovascular risk factors; including diabetes, hypertension, and hyperlipidemia. Posthoc analyses suggest that increased hemodynamic latency in the V3 Left and V3 Right regions predicted reduced overall cognitive ability (WASI-II; IQ measurement). For both the V1 (primary visual cortex) and V3 region (visual association area), specific cognitive domains were sensitive to changes in hemodynamic responses. Specifically, hemodynamic latency in V1 predicted cognitive changes in visuomotor planning, organization and sequencing (DKEFS Tower, and verbal memory (RVALT Delay Recall). Hemodynamic latency in V3 predicted cognitive changes in abstract verbal reasoning (WASI-II Similarities), and semantic verbal fluency (DKEFS Category Fluency).

Our results suggest that increased hemodynamic latency in the healthy visual cortex is associated with reduced cognitive ability. The visual cortex is among the last regions to deteriorate in Alzheimer's disease (Braak stages (Braak et al., 2006). Yet, effective connectivity changes have been shown in the visual cortex of early Alzheimer's disease patients (Rytsar et al., 2011). Decreased processing speed and executive functioning are the hallmark changes associated with healthy aging; with EEG markers of cognitive ability also changing with age (Trammell, MacRae, Davis, Bergstedt, & Anderson, 2017). These patterns of cognitive changes are also characteristic of neurocognitive disorder due to vascular pathology. Studies have shown increase level of white matter hyperintensities in periventricular and subcortical areas, as well as frontal areas (Bahrani et al., 2017) yet few studies have indicated that cerebral blood flow in the visual cortex may lead to a decreased function in cognitive tasks typically associated with higher-order cortices. Our flickering checkboard fMRI paradigm does not involve higher-order cognitive processing, since it is a simple visual stimulus. Cerebral blood flow in the V1 and V3 brain areas predicted ability in cognitive tasks with a strong fronto-executive cognitive load.

Cognitive functioning was assessed with gold-standard neuropsychological tasks typically used in clinical settings. These measures have a robust visual component, including semantic visual presentations. One hypothesis could be that hemodynamic changes in the visual cortex without structural changes may impact the visual processing and visuospatial components typically embedded in neuropsychological assessments, including those assessing fronto-executive functioning. Several studies have extrapolated visuospatial abilities from executive functioning in aging (Whitson et al., 2018), Parkinson's disease (DeGutis et al., 2016; Díaz-Santos, Cao, Mauro, et al., 2015; Díaz-Santos, Cao, Yazdanbakhsh, et al., 2015; Lin et al., 2014; Putcha, Jaywant, & Cronin-Golomb, 2016), and Alzheimer's disease (Cronin-Golomb & Gilmore, 2003). These studies have also explored real-life visuospatial tasks, thus highlighting the intersection between visual and executive functioning to maintain both basic and instrumental activities of daily living (Cronin-Golomb & Gilmore, 2003).

Limitations and Future Studies

There are several limitations to this study. The hemodynamic latency is highly correlated with other hemodynamic response parameters such as decay in the BOLD signal model, and it is possible these may also be associated with cognition. It is important to remember that detailed parameters related to the physiology underlying the BOLD response cannot be determined reliably from just the BOLD signal itself – without additional measurements of that physiology, such as blood flow measured with arterial spin labeling. The patterns observed in the visual cortex associated with reduced cognitive ability may be different elsewhere, as other DCM modeling work has suggested the neurovascular coupling mechanisms are region-specific(Jafarian, Litvak, Cagnan, Friston, & Zeidman, 2019). Nevertheless, analysis with a multi-parameter BOLD model can track subtle differences in the responses across a population through variations in the estimated parameters – and here we found that the latency τ was useful in separating the studied populations. Because of the nature of the model, however, a significant increase of τ in one group could be due to an overall slowing down of the BOLD response (e.g., delayed time to peak) or to a reduced post-stimulus undershoot relative to the positive signal (see Figure 1). That is, underlying changes in the physiology that would lead to either of these observed effects on the BOLD signal could lead to a similar finding of increased τ. Similarly, hemodynamic changes may be a mediator for an unobserved external factor; the relationship of hemodynamic latency with cognition may not be causal. A large number of subjects had incomplete neurocognitive assessments. It is therefore possible that these data were not missing at random and excluding subjects with incomplete data may have introduced some bias. Finally, although this study observed similar relationships between older and younger cohorts, it is still possible that the competing risk still bias our findings. The missing cohort of high-cardiovascular risk individuals – who passed before study enrollment – may have had different relationships than the subjects who survived until old-age.

In summary, in functional MRI (fMRI) studies of aging and disease, the observed blood-oxygen-level dependent (BOLD) signal is assumed to be a convolution of the neuronal stimuli and a hemodynamic response function (HRF). This analyses using a blocked checkerboard stimulus demonstrates that the hemodynamic latency, or transit parameters, may change both with age and cognitive ability, above and beyond all other demographic and stroke risk factors including high cholesterol. Given that the checkerboard task is entirely passive and not cognitively demanding, our results suggest that hemodynamic latency measures were associated with vascular and not cognitive processes. Moreover, it suggests that hemodynamic latency may provide an additional metric (e.g. to complement ASL) for assessing how changes in blood flow may affect current and future cognitive ability. Collectively, these findings suggest that vascular health and cognitive health may share underlying risk factors across the lifespan.

References

Ances, B. M., Liang, C. L., Leontiev, O., Perthen, J. E., Fleisher, A. S., Lansing, A. E., & Buxton, R. B. (2009). Effects of aging on cerebral blood flow, oxygen metabolism, and blood oxygenation level dependent responses to visual stimulation. *Human brain mapping, 30*(4), 1120-1132.

Anstey, K. J., Lipnicki, D. M., & Low, L.-F. (2008). Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *The American journal of geriatric psychiatry, 16*(5), 343-354.

Anttila, T., Helkala, E.-L., Viitanen, M., Kåreholt, I., Fratiglioni, L., Winblad, B., . . . Kivipelto, M. (2004). Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *Bmj, 329*(7465), 539.

Bahrani, A. A., Powell, D. K., Yu, G., Johnson, E. S., Jicha, G. A., & Smith, C. D. (2017). White matter hyperintensity associations with cerebral blood flow in elderly subjects stratified by cerebrovascular risk. *Journal of Stroke and Cerebrovascular Diseases, 26*(4), 779-786.

Birkenhäger, W. H., Forette, F., Seux, M.-L., Wang, J.-G., & Staessen, J. A. (2001). Blood pressure, cognitive functions, and prevention of dementias in older patients with hypertension. *Archives of Internal Medicine, 161*(2), 152-156.

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica, 112*(4), 389-404.

Breteler, M. M. (2000). Vascular risk factors for Alzheimer's disease:: An epidemiologic perspective. *Neurobiology of aging, 21*(2), 153-160.

Buckner, R. L., Snyder, A. Z., Sanders, A. L., Raichle, M. E., & Morris, J. C. (2000). Functional brain imaging of young, nondemented, and demented older adults. *Journal of cognitive neuroscience, 12*(Supplement 2), 24-34.

Buxton, R. B., Uludağ, K., Dubowitz, D. J., & Liu, T. T. (2004). Modeling the hemodynamic response to brain activation. *Neuroimage, 23*, S220-S233.

Chang, C.-C. H., Zhao, Y., Lee, C.-W., & Ganguli, M. (2012). Smoking, death, and Alzheimer's disease: a case of competing risks. *Alzheimer disease and associated disorders, 26*(4), 300.

Claus, J. J., Breteler, M., Hasan, D., Krenning, E., Bots, M., Grobbee, D., . . . Hofman, A. (1998). Regional cerebral blood flow and cerebrovascular risk factors in the elderly population. *Neurobiology of aging, 19*(1), 57-64.

Cronin-Golomb, A., & Gilmore, G. C. (2003). Visual factors in cognitive dysfunction and enhancement in Alzheimer's disease. *Visual information processing*, 3-34.

de la Torre, J. C. (2012). Cerebral hemodynamics and vascular risk factors: setting the stage for Alzheimer's disease. *Journal of Alzheimer's Disease, 32*(3), 553-567.

DeGutis, J., Grosso, M., VanVleet, T., Esterman, M., Pistorino, L., & Cronin-Golomb, A. (2016). Sustained attention training reduces spatial bias in Parkinson's disease: a pilot case series. *Neurocase, 22*(2), 179-186.

Díaz-Santos, M., Cao, B., Mauro, S. A., Yazdanbakhsh, A., Neargarder, S., & Cronin-Golomb, A. (2015). Effect of visual cues on the resolution of perceptual ambiguity in Parkinson's disease and normal aging. *Journal of the International Neuropsychological Society, 21*(2), 146-155.

Díaz-Santos, M., Cao, B., Yazdanbakhsh, A., Norton, D. J., Neargarder, S., & Cronin-Golomb, A. (2015). Perceptual, cognitive, and personality rigidity in Parkinson's disease. *Neuropsychologia, 69*, 183-193.

Dolan, H., Crain, B., Troncoso, J., Resnick, S. M., Zonderman, A. B., & Obrien, R. J. (2010). Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. *Annals of neurology, 68*(2), 231-240.

Dumoulin, S. O., & Wandell, B. A. (2008). Population receptive field estimates in human visual cortex. *Neuroimage, 39*(2), 647-660.

Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *American journal of epidemiology, 138*(6), 353-364.

Evans, R., Emsley, C., Gao, S., Sahota, A., Hall, K., Farlow, M., & Hendrie, H. (2000). Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. *Neurology, 54*(1), 240-240.

Evans, R., Hui, S., Perkins, A., Lahiri, D., Poirier, J., & Farlow, M. (2004). Cholesterol and APOE genotype interact to influence Alzheimer disease progression. *Neurology, 62*(10), 1869-1871.

Friston, K. J., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *Neuroimage, 19*(4), 1273-1302.

Friston, K. J., Mechelli, A., Turner, R., & Price, C. J. (2000). Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics. *Neuroimage, 12*(4), 466-477.

Girouard, H., & Iadecola, C. (2006). Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. *Journal of applied physiology, 100*(1), 328-335.

Gröschel, K., Terborg, C., Schnaudigel, S., Ringer, T., Riecker, A., Witte, O., & Kastrup, A. (2007). Effects of physiological aging and cerebrovascular risk factors on the hemodynamic response to brain activation: a functional transcranial Doppler study. *European journal of neurology, 14*(2), 125-131.

Hamzei, F., Knab, R., Weiller, C., & Röther, J. (2003). The influence of extra-and intracranial artery disease on the BOLD signal in FMRI. *Neuroimage, 20*(2), 1393-1399.

Heinzle, J., Koopmans, P. J., den Ouden, H. E., Raman, S., & Stephan, K. E. (2016). A hemodynamic model for layered BOLD signals. *Neuroimage, 125*, 556-570.

Hirao, K., Ohnishi, T., Hirata, Y., Yamashita, F., Mori, T., Moriguchi, Y., . . . Yamada, M. (2005). The prediction of rapid conversion to Alzheimer's disease in mild cognitive impairment using regional cerebral blood flow SPECT. *Neuroimage, 28*(4), 1014-1021.

Jafarian, A., Litvak, V., Cagnan, H., Friston, K. J., & Zeidman, P. (2019). Neurovascular coupling: insights from multi-modal dynamic causal modelling of fMRI and MEG. *arXiv preprint arXiv:1903.07478*.

Jarvik, G. P., Wijsman, E. M., Kukull, W. A., Schellenberg, G., Yu, C., & Larson, E. B. (1995). Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease A case-control study. *Neurology, 45*(6), 1092-1096.

Johnston, S. C., & Hauser, S. L. (2010). The challenge of publishing newsworthy epidemiology. *Annals of neurology, 68*(2), A8-A10.

Kuźma, E., Lourida, I., Moore, S. F., Levine, D. A., Ukoumunne, O. C., & Llewellyn, D. J. (2018). Stroke and dementia risk: A systematic review and meta-analysis. *Alzheimer's & Dementia*.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., & Nangia, V. (1998). Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology, 35*(2), 199-210.

Launer, L. J., Masaki, K., Petrovitch, H., Foley, D., & Havlik, R. J. (1995). The association between midlife blood pressure levels and late-life cognitive function: the Honolulu-Asia Aging Study. *Jama, 274*(23), 1846-1851.

Leuba, G., & Kraftsik, R. (1994). Changes in volume, surface estimate, three-dimensional shape and total number of neurons of the human primary visual cortex from midgestation until old age. *Anatomy and embryology, 190*(4), 351-366.

Lin, C.-C., Wagenaar, R. C., Young, D., Saltzman, E. L., Ren, X., Neargarder, S., & Cronin-Golomb, A. (2014). Effects of Parkinson's disease on optic flow perception for heading direction during navigation. *Experimental brain research, 232*(4), 1343-1355.

McGuinness, B., Todd, S., Passmore, P., & Bullock, R. (2009). Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database of Systematic Reviews*(4).

Mentis, M. J., Horwitz, B., Grady, C. L., Alexander, G. E., VanMeter, J. W., Maisog, J. M., . . . Rapoport, S. I. (1996). Visual cortical dysfunction in Alzheimer's disease evaluated with a temporally graded" stress test" during PET. *Am J Psychiatry*.

Muldoon, M. F., Ryan, C. M., Matthews, K. A., & Manuck, S. B. (1997). Serum cholesterol and intellectual performance. *Psychosomatic medicine, 59*(4), 382-387.

Nobili, F., Rodriguez, G., Marenco, S., De Carli, F., Gambaro, M., Castello, C., . . . Rosadini, G. (1993). Regional cerebral blood flow in chronic hypertension. A correlative study. *Stroke, 24*(8), 1148-1153.

Nooner, K. B., Colcombe, S. J., Tobe, R. H., Mennes, M., Benedict, M. M., Moreno, A. L., . . . Li, Q. (2012). The NKI-Rockland sample: a model for accelerating the pace of discovery science in psychiatry. *Frontiers in neuroscience, 6*.

Notkola, I.-L., Sulkava, R., Pekkanen, J., Erkinjuntti, T., Ehnholm, C., Kivinen, P., . . . Nissinen, A. (1998). Serum Total Cholesterol, Apolipoprotein E {FC12} e4 Allele, and Alzheimer's Disease. *Neuroepidemiology, 17*(1), 14-20.

Novak, V. (2012). Cognition and hemodynamics. *Current cardiovascular risk reports, 6*(5), 380-396.

Novak, V., & Hajjar, I. (2010). The relationship between blood pressure and cognitive function. *Nature Reviews Cardiology, 7*(12), 686.

Østergaard, L., Aamand, R., Gutiérrez-Jiménez, E., Ho, Y.-C. L., Blicher, J. U., Madsen, S. M., . . . Møller, A. (2013). The capillary dysfunction hypothesis of Alzheimer's disease. *Neurobiology of aging, 34*(4), 1018-1031.

Penny, W. D., Friston, K. J., Ashburner, J. T., Kiebel, S. J., & Nichols, T. E. (2011). *Statistical parametric mapping: the analysis of functional brain images*: Elsevier.

Pineiro, R., Pendlebury, S., Johansen-Berg, H., & Matthews, P. (2002). Altered hemodynamic responses in patients after subcortical stroke measured by functional MRI. *Stroke, 33*(1), 103-109.

Putcha, D., Jaywant, A., & Cronin-Golomb, A. (2016). Cognitive and Perceptual Impairments in Parkinson's Disease Arising from Dysfunction of the Cortex and Basal Ganglia *The Basal Ganglia* (pp. 189-216): Springer.

Riecker, A., Grodd, W., Klose, U., Schulz, J. B., Gröschel, K., Erb, M., . . . Kastrup, A. (2003). Relation between regional functional MRI activation and vascular reactivity to carbon

dioxide during normal aging. *Journal of Cerebral Blood Flow & Metabolism, 23*(5), 565-573.

Rigoux, L., Stephan, K. E., Friston, K. J., & Daunizeau, J. (2014). Bayesian model selection for group studies—revisited. *Neuroimage, 84*, 971-985.

Robbins, M. A., Elias, M. F., Elias, P. K., & Budge, M. M. (2005). Blood pressure and cognitive function in an African-American and a Caucasian-American sample: the Maine-Syracuse Study. *Psychosomatic medicine, 67*(5), 707-714.

Rytsar, R., Fornari, E., Frackowiak, R. S., Ghika, J. A., & Knyazeva, M. G. (2011). Inhibition in early Alzheimer's disease: an fMRI-based study of effective connectivity. *Neuroimage, 57*(3), 1131-1139.

Schmidt, M. (1996). *Rey auditory verbal learning test: A handbook*: Western Psychological Services Los Angeles, CA.

Smith, A. T., Greenlee, M. W., Singh, K. D., Kraemer, F. M., & Hennig, J. (1998). The processing of first-and second-order motion in human visual cortex assessed by functional magnetic resonance imaging (fMRI). *Journal of Neuroscience, 18*(10), 3816-3830.

Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J., & Whitmer, R. A. (2009). Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dementia and geriatric cognitive disorders, 28*(1), 75-80.

Stano, J. F. (2004). Wechsler abbreviated scale of intelligence. *Rehabilitation Counseling Bulletin, 48*(1), 56.

Stephan, K. E., Penny, W. D., Daunizeau, J., Moran, R. J., & Friston, K. J. (2009). Bayesian model selection for group studies. *Neuroimage, 46*(4), 1004-1017.

Sue Baron, I. (2004). Delis-Kaplan executive function system. *Child Neuropsychology, 10*(2), 147-152.

Trammell, J. P., MacRae, P. G., Davis, G., Bergstedt, D., & Anderson, A. E. (2017). The relationship of cognitive performance and the theta-alpha power ratio is age-dependent: an EEG study of short term memory and reasoning during task and resting-state in healthy young and old adults. *Frontiers in aging neuroscience, 9*, 364.

Wan, X., Riera, J., Iwata, K., Takahashi, M., Wakabayashi, T., & Kawashima, R. (2006). The neural basis of the hemodynamic response nonlinearity in human primary visual cortex: Implications for neurovascular coupling mechanism. *Neuroimage, 32*(2), 616-625.

Wang, L., Mruczek, R. E., Arcaro, M. J., & Kastner, S. (2014). Probabilistic maps of visual topography in human cortex. *Cerebral Cortex, 25*(10), 3911-3931.

West, K. L., Zuppichini, M. D., Turner, M. P., Sivakolundu, D. K., Zhao, Y., Abdelkarim, D., . . . Rypma, B. (2019). BOLD hemodynamic response function changes significantly with healthy aging. *Neuroimage, 188*, 198-207.

Whitson, H. E., Cronin-Golomb, A., Cruickshanks, K. J., Gilmore, G. C., Owsley, C., Peelle, J. E., . . . Yaffe, K. (2018). American Geriatrics Society and National Institute on Aging Bench-to-Bedside Conference: Sensory Impairment and Cognitive Decline in Older Adults. *Journal of the American Geriatrics Society, 66*(11), 2052-2058.

Wierenga, C. E., Dev, S. I., Shin, D. D., Clark, L. R., Bangen, K. J., Jak, A. J., . . . Bondi, M. W. (2012). Effect of mild cognitive impairment and APOE genotype on resting cerebral blood flow and its association with cognition. *Journal of Cerebral Blood Flow & Metabolism, 32*(8), 1589-1599.

Wierenga, C. E., Hays, C. C., & Zlatar, Z. Z. (2014). Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *Journal of Alzheimer's Disease, 42*(s4), S411-S419.

Wu, L.-T., McNeely, J., Subramaniam, G. A., Sharma, G., VanVeldhuisen, P., & Schwartz, R. P. (2016). Design of the NIDA clinical trials network validation study of tobacco, alcohol, prescription medications, and substance use/misuse (TAPS) tool. *Contemp Clin Trials, 50*, 90-97.

Zeidman, P., Jafarian, A., Corbin, N., Seghier, M. L., Razi, A., Price, C. J., & Friston, K. J. (2019). A tutorial on group effective connectivity analysis, part 1: first level analysis with DCM for fMRI. *arXiv preprint arXiv:1902.10597*.

Zhou, J., Yu, J.-T., Wang, H.-F., Meng, X.-F., Tan, C.-C., Wang, J., . . . Tan, L. (2015). Association between stroke and Alzheimer's disease: systematic review and meta-analysis. *Journal of Alzheimer's Disease, 43*(2), 479-489.

Variable	Estimate	Std. Error	t-value	Pr(>|t|)	Significance
(Intercept)	69.148	6.232	11.096	0.000	***
Age	0.005	0.045	0.102	0.918	
Male Sex	2.165	1.263	1.714	0.087	.
Years of Education	1.930	0.318	6.065	0.000	***
Race: Other	4.385	9.914	0.442	0.659	
Race: White	6.849	5.012	1.366	0.173	
Socio-Economic Status	-0.002	0.105	-0.023	0.981	
Cardiac Diagnoses	3.278	1.329	2.467	0.014	*
Heavy Alcohol Use	-2.736	1.258	-2.175	0.030	*
High Cholesterol	3.864	1.389	2.782	0.006	**
Hypertension	0.227	1.548	0.147	0.883	
Type 2 Diabetes	-2.989	2.719	-1.099	0.272	
BMI	-0.191	0.107	-1.789	0.074	.
Smoking	0.849	1.602	0.530	0.596	
Transit V1 Left	-3.725	5.070	-0.735	0.463	
Transit V1 Right	-3.890	5.009	-0.776	0.438	
Transit V3 Left	-11.274	5.573	-2.023	0.044	*
Transit V3 Right	-14.750	5.790	-2.548	0.011	*
Other: Socioeconomic Status	-0.146	0.265	-0.549	0.583	
White: Socioeconomic Status	0.054	0.115	0.470	0.639	

Table 1: Increased transit time in the V3 left and right cortical regions was associated with reduced cognitive ability, independent of all other cerebrovascular and demographic covariates. Alcohol use was associated with reduced overall cognitive functioning (IQ 2.8 pts, p<0.05) while cardiac disorders (3.3 IQ pts; p<0.05), high cholesterol (3.9 pts; p<0.05), and years of education (2 IQ pts/year; p<0.001) were associated with higher general cognitive ability holding constant all else.

Assessment	Raw Variables	Hemisphere	Significance
DKEFS- Tower	Total Achievement Score Total Raw	L	*
DKEFS- Letter Fluency	Letter Fluency Raw		
DKEFS- Category Fluency	Category Fluency Raw	R	*
DKEFS- Category Switching Fluency	Category Switching Raw		
DKEFS-Trails - Visual Scanning	Visual Scanning (Time)		
DKEFS-Trails - Number Sequencing	Number Sequencing (Time)		
DKEFS-Trails - Letter Sequencing	Letter Sequencing (Time)	L	*
DKEFS-Trails - Number-Letter Switching	Number-Letter Switching (Time)		
DKEFS-Trails - Motor Speed	Motor Speed (Time)	L	*
RAVLT	Delay - Total Correct	R	*
WASI	full scale IQ composite score	L,R	*,*
WASI-II Vocabulary	Vocabulary Raw Score		
WASI-II Block Design	Block Design Raw Score		
WASI-II Matrix Reasoning	Matrix Reasoning Raw Score		
WASI-II Similarities	Similarities Raw Score	L, R	**,*

Table 2: Both general cognitive ability (IQ) and specific cognitive domains were assessed. Our results suggest that increased hemodynamic latency in the V3 Left and V3 Right regions predicted reduced overall cognitive ability (WASI-II; IQ measurement). Specific domains were also found. See discussion for more information.

Figure Legends

Figure 1: The Hemodynamic Response Function is the regional Blood Oxygenation Level Dependent (BOLD) response generated from a brief peripheral stimulus, created through a sequence of vascular and metabolic dynamics. The transit time reflects the ratio of resting cerebral blood volume to resting cerebral blood flow. Doubling the transit time (solid line) attenuates both the overshoot and undershoot of the HRF, while also delaying the time to peak for the BOLD signal.   Figure adapted from (Friston et al., 2000).

Figure 2: Competing models of connectivity, compared using Bayesian model selection.   We used dynamic causal modeling to model the regional coupling in the visual cortex in response to a checkerboard visual stimulus.   Using Bayesian model selection, Model C1 was selected as the optimal architecture, while M5 was the best model of modulatory effects.

Figure 3: Using Bayesian parameter averaging, the posterior distributions of the transit and decay parameters for each group showed differences between the older (>=60) and younger (<60) age groups. The transit time (hemodynamic latency) was increased for older subjects.

Figure 4: Within late middle-aged adults aged 50-65, we compared connectivity between low and high-functioning individuals. Cross-hemispheric effective connectivity differed between high functioning and low-functioning older adults ($p<0.05$) on the WASI-II Similarities Raw Score (SRS), with the V3 regions showing significant differences in both effective connectivity and modulatory effects ($p<0.05$). Group-level estimates for the effective connectivity and modulatory effects for the C1-M5 model. Labels for the edges are of the form (estimated) mean +/- (estimated) standard deviation.